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The role of high-dose-rate brachytherapy boost in breast-conserving therapy: Long-term results of the Hungarian National Institute of Oncology

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ABSTRACT

Aim: To report the long-term results of high-dose-rate (HDR) brachytherapy (BT) boost for breast cancer patients treated with conservative surgery and radiotherapy.
Materials and methods: Between 1995 and 2007, 100 early-stage breast cancer patients received an HDR BT boost after conservative surgery and whole breast irradiation. Ten patients (10%) received a single-fraction HDR boost of 8–10.35 Gy using rigid needles, while 90 (90%) were treated with a fractionated multi-catheter HDR BT boost. The latter consisted of 3×4 Gy ($n = 19$), 3×4.75 Gy ($n = 70$), and 2×6.4 Gy ($n = 1$). Breast cancer related events, cosmetic results and side effects were assessed.
Results: At a median follow-up time of 94 months (range: 8–152) only 7 (7%) ipsilateral breast failures were observed for a 5- and 8-year actuarial rate of 4.5 and 7.0%, respectively. The 8-year disease-free, cancer-specific, and overall survival was 76.1, 82.8, and 80.4%, respectively. Cosmetic outcome was rated excellent in 17%, good in 39%, fair in 33%, and poor in 11%. Data on late radiation side effects were available for 91 patients (91%). Grade 3 fibrosis and grade 3 telangiectasia occurred in 6 (6.6%) and 2 (2.2%) patients, respectively. In univariate analysis only positive margin status had a significant negative effect on local control.
Conclusions: HDR BT boost using multi-catheter implants produce excellent long-term local tumour control with acceptable cosmetic outcome and low rate of grade 3 late radiation side effects.

1. Background

Over the last decades, breast-conserving surgery (BCS) and postoperative radiotherapy (RT) became the standard of care for the treatment of early-stage breast carcinoma.[1,2] The standard technique of RT after BCS is to treat the whole breast by teletherapy via tangential fields up to a total dose of 45–50 Gy.[3] The main rationale to give an additional dose of 10–25 Gy to the tumour bed after whole breast irradiation (WBI) was based on the clinical observation that 67–100% of ipsilateral breast recurrences originated from the vicinity of the original index

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lesion.[4] To date, three randomized trials have confirmed that a boost dose of 10–16 Gy after 50 Gy WBI significantly decreased the local recurrence (LR) rate.[4–8] Patient age less than 50 years, close, microscopically positive or unknown surgical margins, and the presence of an extensive intraductal component (EIC) are generally accepted as absolute indications for boost irradiation.[4] However, a controversy still exists regarding the optimal boost technique. Traditionally, low-dose-rate (LDR) brachytherapy (BT), electrons or photons have been used to deliver the boost dose to the tumour bed.[4,5,8–15] Later, high-dose-rate (HDR) BT has also been accepted as a safe alternative boost modality.[6,7,12,16–27]

2. Aim

A retrospective analysis was performed to report the long-term results of HDR BT boost for breast cancer patients treated with BCS and RT at the Hungarian National Institute of Oncology (HNIO).

3. Materials and methods

3.1. *Surgery, patient and tumour characteristics*

Between 1995 and 2007, 100 early-stage breast cancer patients received an HDR BT boost after conservative surgery and WBI. All patients underwent wide excision, defined as a resection of the primary tumour with at least 1 cm of macroscopic free margin. During surgery, the boundaries of the excision cavity were marked with titanium clips. At least level I–II axillary dissection was performed for 84 patients (84%) and 12 women (12%) underwent sentinel lymph node biopsy. For the remaining 4 cases (4%), operated on for pure ductal carcinoma in situ (DCIS), surgical axillary staging was omitted by the surgeon's preference. Patient and tumour characteristics are listed in Table 1.

Table 1 – Patient and tumour characteristics.

Characteristic	n (%)
Mean age (years)	56.7
Range	37–77
Age (years)	
<40	5 (5%)
40–50	22 (22%)
>50	73 (73%)
Premenopausal	30 (30%)
Histological type	
DCIS	6 (6%)
Ductal	67 (67%)
Lobular	16 (16%)
Ductal + lobular	2 (2%)
Mucinous	4 (4%)
Medullary	2 (2%)
Tubular	1 (1%)
Apocrin	1 (1%)
Metaplastic	1 (1%)
Surgical margins	
Positive	5 (5%)
Close (≤2 mm)	13 (13%)
Clear (>2 mm)	69 (69%)
UK	13 (13%)
Pathologic tumour size (mm)	
Mean	18.2
Range	1–35
pTis	6 (6%)
pT1	57 (57%)
pT2	37 (37%)
Pathologic nodal status	
pN0 (ALND)	59 (59%)
pN0 (SLNB)	11 (11%)
pN1mi (SLNB)	1 (1%)
pN1a (ALND)	16 (16%)
pN2a (ALND)	7 (7%)
pN3a (ALND)	2 (2%)
pNx (cN0)[a]	4 (4%)
HG	
1	20 (20%)
2	39 (39%)
3	27 (27%)
NA[b]	6 (6%)
UK	8 (8%)
LVI	
Positive	31 (31%)
Negative	60 (60%)
UK	9 (9%)
EIC	
Positive	21 (21%)
Negative	58 (58%)
NA[b]	6 (6%)
UK	15 (15%)
ER status	
Positive	59 (59%)
Negative	30 (30%)
UK	11 (11%)
PR status	
Positive	54 (54%)
Negative	34 (34%)
UK	12 (12%)

DCIS = ductal carcinoma in situ; UK = unknown; ALND = axillary lymph node dissection; SLNB = sentinel lymph node biopsy; HG = histological grade. LVI = lympho-vascular invasion; EIC = extensive intraductal carcinoma; ER = estrogen receptor; PR = progesterone receptor. Data presented as number of patients, with percentage in parentheses, unless otherwise noted.

[a] Surgical axillary staging was omitted in 4 out of 6 patients with DCIS.

[b] NA = not applicable (for DCIS).

3.2. *External beam irradiation*

All patients received WBI delivered with telecobalt ($n = 5$) or 6–9 MV photon ($n = 95$) beams using wedged tangential fields with 2 Gy daily fractions (5 fractions/week). The dose was prescribed to 95% of the dose at the isocentre, which was located on the central axis CT slice at the midpoint between the lung–chest wall interface and skin surface. The median total dose of WBI was 50 Gy (range: 30–50 Gy). Seventy-five out of 100 patients (75%) received the full intended total dose of 50 Gy. In 25 patients (25%) the total dose was limited to 30 Gy ($n = 1$), 38 Gy ($n = 1$), 44 Gy ($n = 4$), 46 Gy ($n = 10$), and 48 Gy ($n = 9$) based on the decision of the treating radiation oncologist. Twenty-five axillary lymph node-positive patients (25%) received 44–50 Gy (median: 50 Gy) regional nodal irradiation using an anterior supraclavicular–axillary 6–9 MV photon field.

3.3. *HDR brachytherapy boost*

Interstitial BT boost was performed 2–3 weeks after completing WBI. Patients were treated with HDR remote afterloading

Table 2 – Biologically equivalent HDR fractionation schedules used for brachytherapy boost calculated by the linear-quadratic model.

Low boost dose group ($n = 21$) 20 Gy LDR-equivalent fractionation schemes (calculated for late effects; α/β ratio = 4 Gy)	High boost dose group ($n = 79$) 20 Gy LDR-equivalent fractionation schemes (calculated for early effects; α/β ratio = 10 Gy)
1×8 Gy ($n = 2$)	1×10.35 Gy ($n = 8$)
2×5.2 Gy (not used)	2×6.4 Gy ($n = 1$)
3×4 Gy ($n = 19$)	3×4.75 Gy ($n = 70$)

equipment (microSelectron Classic and V2, Nucletron B.V., Veenendaal, The Netherlands) using an ^{192}Ir stepping source with 370 GBq initial activity. The implantations were performed under local anaesthesia. Pre-implant X-ray simulation was performed with a template on the breast to define the entrance and exit points of the needles according to the projections of surgical clips of the tumour bed using the needle-eye-view technique. The planning target volume (PTV) was defined as the excision cavity with a margin of 1–2 cm. Following pre-implant simulation 3–19 guide needles (median: 6.5) were inserted into the previously targeted volume in a triangular setting using template guidance with 13–15 mm spacing between the needles. Single-, double-, triple-, and four-plane implants were performed on 3 (3%), 82 (82%), 11 (11%), and 4 (4%) of the patients, respectively. The HDR fractionation schedules were calculated using the linear-quadratic (LQ) model with an α/β ratio of 4 Gy for late and 10 Gy for early effects. [28] The biologically equivalent HDR fractionation schedules used for the HDR BT boost calculated by the LQ model are summarized in Table 2. For the first 21 patients (low boost dose group), the boost dose was calculated to be equivalent to the late effects of 20 Gy LDR radiation. Since serious side effects were not observed, the total boost dose was increased for the next 79 patients (high boost dose group) to be equivalent to the early (tumour) effects of 20 Gy LDR treatment. Overall, 10 patients (10%) received a single-fraction HDR BT boost of 8 Gy ($n = 2$) and 10.35 Gy ($n = 8$) using rigid needles, while 90 (90%) were treated with fractionated HDR schedules using flexible plastic tubes (multi-catheter technique). The latter consisted of 3×4 Gy ($n = 19$), 3×4.75 Gy ($n = 70$), and 2×6.4 Gy ($n = 1$) using 1 fraction daily over 2–3 days. Patients receiving 2 or 3 fractions stayed in hospital for 1–2 nights. For fractionated multi-catheter treatments the guide needles were replaced with plastic catheters and secured with fixation buttons. The dose planning was based on three-dimensional reconstruction of the catheters (or needles), surgical clips, and skin points with the help of two post-implant isocentric X-ray images, using the variable angle reconstruction technique. The active source positions and reference dose points were defined individually in each catheter, and optimization of the dwell times to dose points and geometry was performed. The most peripheral active source positions were kept at a minimum of 10 mm distance from the skin points, limiting the maximal skin dose to 60% of the prescribed dose. The distance of the dose points from the catheters was 5–13 mm, varying from catheter to catheter to achieve 100% isodose surface cover for all surgical clips with a margin of 1–2 cm. For the assessment of implant quality, cumulative dose-volume histogram and dose non-uniformity ratio (DNR) were used. The mean volume encompassed by the 100% isodose surface was 43.5 cm^3 (range: 18.9–104.2 cm^3). The mean DNR was 0.49 (range: 0.30–0.58). Pre- and post-implant CT scans were used for BT treatment planning only for 5 patients (5%).

3.4. *Adjuvant systemic therapy*

Systemic therapy was given according to the actual institutional treatment protocol. Adjuvant therapy has evolved over the years. Systemic therapy for low-risk patients with pT1 pN0 tumours was optional rather than mandatory before the publication of the guidelines of the 1998 St. Gallen's Consensus Conference.[29] Since 1999, all patients with tumour size >10 mm have received adjuvant systemic therapy. Thus, overall, 62 patients (62%) received systemic therapy, 42 (42%) hormone therapy, 9 (9%) chemo- and hormone therapy, and 11 (11%) chemotherapy alone. Hormone therapy consisted of aromatase inhibitors ($n = 26$) or tamoxifen ($n = 25$) with goserelin acetate ($n = 3$) for premenopausal women. Patients receiving chemotherapy were treated with cyclophosphamide, methotrexate and fluorouracil (CMF; $n = 12$) or an anthracycline-based regimen ($n = 8$).

3.5. *Follow-up and statistical analysis*

The median follow-up for all patients was 90.5 months (range: 7–152 months) and 94 months (range: 8–152 months) for surviving patients. Patients were seen every 3 months in the first 2 years after the treatment and every 6 months thereafter. Mammography, breast and abdominal ultrasound examinations, chest X-ray, and blood tests were performed annually. In case of uncertain mammography and ultrasound findings, breast MRI and/or aspiration cytology of suspicious lesions were performed to differentiate between LR and localized fibrosis or fat necrosis. LR was defined as any detection of cancer in the treated breast, proved by histological examination. All intra-breast relapses, before or after the detection of distant metastasis, were taken into account. An elsewhere breast failure (EBF) was defined as an ipsilateral LR detected at least 2 cm from the surgical clips. All other intra-breast recurrences were classified as true recurrence/marginal miss (TR/MM). The cosmetic results and late side effects were evaluated retrospectively. Cosmetic results were assessed using the Harvard criteria.[30] Skin side effects and fibrosis were scored by the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer (RTOG/EORTC) late radiation morbidity scoring scheme.[31] All available mammography films were carefully reviewed for asymptomatic fat necrosis (i.e. oil-cysts and/or coarse calcifications).

All intervals were calculated from the date of surgery. The actuarial rates of specific events and survival were calculated using the Kaplan–Meier method.[32] Univariate Cox regression analysis was used to evaluate the possible prognostic factors

Table 3 – Incidence of first events.

Event	*n* (%)
Local recurrence	7 (7%)
TR/MM	2 (2%)
EBF	5 (5%)
Regional recurrence	1 (1%)
Supraclavicular failure	1 (1%)
Axillary failure	0 (0%)
Distant metastasis	15 (15%)
Any first relapse[a]	23 (23%)
Contralateral breast cancer	2 (2%)
Second primary malignancy	5 (5%)
Non-breast cancer death	2 (2%)

TR/MM = true recurrence/marginal miss; EBF = elsewhere breast failure.
[a] Any first relapse = local, regional, or distant failure, whichever came first.

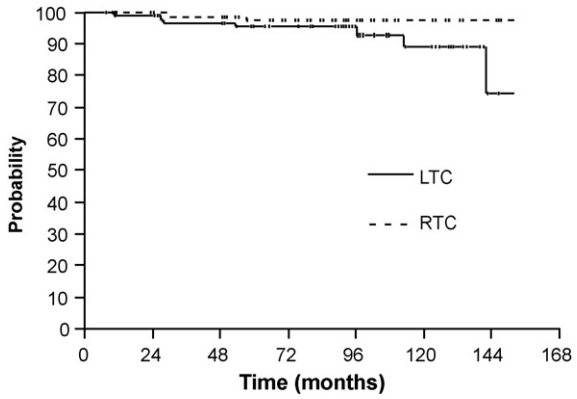

Fig. 1 – Time to local and regional recurrence by Kaplan–Meier estimates. LTC = local tumour control; RTC = regional tumour control. 8-year LTC = 93.0%. 8-year RTC = 97.6%.

for LR.[33] A *p*-value of ≤0.05 was considered statistically significant. A trend to significance was established at *p* values >0.05–0.10. SOLO software (Department of Biometrics, University of California, Los Angeles, CA, USA) was used for statistical analyses.

4. Results

4.1. *Treatment outcome*

Overall, 7 patients (7%) developed ipsilateral breast failure and all LR occurred as a first event. LRs were classified as TR/MM and EBF in 2 (2%) and 5 (5%) cases, respectively. Mean time to TR/MM and EBF was 31.5 months (range: 10–53) and 81.2 months (range: 27–142), respectively. The crude rates of first events are summarized in Table 3. The 5- and 8-year actuarial rate of LR was 4.5 and 7.0% (Fig. 1). The 8-year probability of developing TR/MM and EBF was 2.2 and 4.8%, respectively. The 8-year LR rate with clear (>2 mm), close (≤2 mm), unknown, and positive margin status was 4.9, 0, 0, and 46.7%, respectively. A total of 2 (2%) regional nodal failures were observed for an 8-year actuarial rate of 2.4% (Fig. 1). Both regional nodal failures occurred as a supraclavicular failure. Axillary recurrence was not observed during the follow-up period. Disease-free survival (DFS), cancer-specific survival (CSS), and overall survival (OS) at 8 years were 76.1, 82.8, and 80.4%, respectively.

4.2. *Salvage treatment and outcome for LR*

Overall, at a median follow-up of 35 months (range: 3–120 months) after LR, five out of 7 patients (71.4%) were alive. One patient with an inoperable diffuse multiplex LR received palliative chemotherapy and died of the disease 39 months after LR. The other 6 patients with LR were salvaged with repeated BCS ($n = 4$) or mastectomy ($n = 2$). At the time of analysis 2 patients in the re-excision group and 1 patient in the mastectomy group were alive without any further relapse at 20–120 months after LR. The other 3 women (2 in the re-excision and 1 in the mastectomy groups) developed a second LR and subsequent distant metastases later and were treated with systemic treatments. Two of them were alive with the disease 3 and 35 months after LR and 1 woman died of her disease 56 months after LR.

4.3. *Prognostic factors for LR*

On univariate analysis, among the evaluated patient- and tumour-related parameters (e.g. menopausal status, age groups: ≤50 years vs. older, oestrogen and progesterone receptor status, histological type: ductal vs. all others, presence of extensive intraductal component (EIC): yes vs. no, margin status: negative vs. positive and clear (>2 mm) vs. close (≤2 mm), tumour size: pT1 vs. pT2, histological and nuclear grade: grade 1–2 vs. 3) only positive margin status was significantly associated with the development of LR ($p = 0.007$; 8-year LR rate with negative and positive margins: 4.2% vs. 46.7%, respectively). There was also a non-significant trend for a higher LR rate for patients with EIC positive tumours ($p = 0.067$; 8-year LR rate with EIC negative and positive tumours: 3.7% vs. 24.0%, respectively). However, there was no significant difference in local tumour control between patients with clear (>2 mm) and close (≤2 mm) surgical margins.

Among treatment-related parameters (e.g. number of implant needles, number of implant planes, tumour bed dose: low vs. high boost dose, and use of adjuvant systemic therapy) there was a non-significant trend for higher LR rate for those patients treated with a lower tumour bed dose ($p = 0.073$; 8-year LR rate with low and high boost dose groups: 23.7% vs. 1.3%, respectively).

Due to the low number of events ($n = 2$), no parameter was significantly associated with the development of TR/MM. However, both true recurrences occurred in patients having EIC positive tumours, associated with positive margins in one case.

Table 4 – Cosmetic results and late radiation side effects.

Variable	*n* (%)
Cosmetic results ($n = 66$)[a]	
Excellent	11 (17%)
Good	26 (39%)
Fair	22 (33%)
Poor	7 (11%)
Skin side effects ($n = 91$)[b]	
Grade 0	67 (74%)
Grade 1	11 (12%)
Grade 2	11 (12%)
Grade 3	2 (2%)
Fibrosis ($n = 91$)[b]	
Grade 0	36 (39%)
Grade 1	26 (29%)
Grade 2	23 (25%)
Grade 3	6 (7%)
Fat necrosis ($n = 100$)	
Asymptomatic	24 (24%)
Symptomatic	2 (2%)

[a] Data on cosmetic results were available for 66 patients.
[b] Data on late radiation side effects were available for 91 patients.

4.4. *Cosmetic results and side effects*

Data on late radiation side effects were available for 91 patients (91%). Cosmetic results were documented for 66 patients (66%). Cosmetic results and late radiation side effects are listed in Table 4. The rate of excellent/good cosmetic outcomes was 56.1%. Severe (≥grade 3) side effects occurred in only 8 patients (8%), including 6 cases (6%) with grade 3 fibrosis and 2 (2%) with grade 3 telangiectasia. Neither of the 2 symptomatic fat necroses required surgical intervention.

5. Discussion

The standard technique of RT after BCS is to treat the whole breast by teletherapy with tangential fields up to a total dose of 45–50 Gy supplemented with an additional dose of 10–25 Gy to the tumour bed for selected high-risk patients.[3,4] Based on the analysis of dose–response curves, Van Limbergen[34] reported that above 50 Gy, an increase of 15 Gy would reduce the LR rate by a factor of 2. To date, three randomized trials have confirmed that a boost dose of 10–16 Gy after 50 Gy WBI significantly decreased the LR rate (Table 5).[4–8] Patient age less than 50 years, close, microscopically positive or unknown surgical margins, and the presence of an extensive intraductal component (EIC) are generally accepted as absolute indications for boost irradiation.[4,34] However, a controversy still exists regarding the optimal boost technique. Traditionally, LDR BT or teletherapy using electron or photon beams has been used to deliver the boost dose to the tumour bed.[5,8–15,34] Later, HDR BT was also accepted as a safe alternative boost modality (Table 6).[4,6,7,12,16–27,34] Only a few reports have compared the outcome in patients treated with BT or external beam boost.[6,7,9–15,20,21,25,35,36] In the majority of these studies similar local control and cosmetic results have been reported for women boosted either with interstitial implants or electrons/photons. Recently, Knauerhase et al.[25] reported that a median dose of 10 Gy HDR BT boost yielded a significantly lower 10-year actuarial LR rate compared to an external beam boost (5.9% vs 12.5%; $p = 0.023$). In the EORTC boost trial the 10-year cumulative incidence of LR was 6.3% for the 1639 patients who received an electron boost, 5.3% in the 753 patients who received a photon boost and only 3.7% in the 225 patients who had an interstitial LDR BT boost.[36] The difference was not significant ($p = 0.13$); however, the trial was not powered to detect a possible difference in local control between different boost modalities.

Based on our results, it seems that an interstitial HDR BT boost can be used in the conservative therapy of breast cancer with low incidence of late side effects and with at least similar local tumour control as with percutaneous boost techniques. The relatively low rate (56%) of good/excellent cosmetic results can be explained by the relatively high (20 Gy LDR-equivalent) boost dose and high DNR value. On the other hand, this high dose of HDR BT boost was able to mask classical risk factors for LR with the exception of positive margin status. Furthermore, BT is preferable in some anatomical situations, especially in cases of a deep-seated tumour bed in a large volume breast. Obviously, BT offers the practical advantage of more conformal treatment of small volumes with higher doses and lower doses to the skin.[4,34] Van Limbergen[34] compared dose distributions of 4.5–15 MeV electron boosts to different settings of interstitial implants. He found that for target depths reaching beyond 28 mm under the skin, interstitial implants had a ballistic advantage, delivering significantly lower skin doses than electron beams. Thus, in addition to external beam boost modalities multi-catheter HDR BT remains a standard treatment option to deliver an additional dose to the tumour bed after BCS and WBI.

Table 5 – Results of randomized "boost versus no boost" trials.

Clinical trial	Patient no.	Technique	Boost dose (Gy)	Median FUP (years)	5-Year LR boost vs. no boost (%)	10-Year LR boost vs. no boost (%)	*p*-Value
EORTC[5]	5318	EBI/LDR BT	15–16	10.8	4.3 vs. 7.3	6.2 vs. 10.2	<0.0001
HNIO[4,6,7]	627	ELE/HDR BT	12–16	5	6.3 vs. 13.3	NR	0.0017
Lyon[8]	1024	ELE	10	3.3	3.6 vs. 4.5	NR	0.044

EORTC = European Organization for Research and Treatment of Cancer; HNIO = Hungarian National Institute of Oncology; FUP = follow-up period; LR = local recurrence; EBI = external beam irradiation (photons or electrons); ELE = electrons; LDR = low-dose-rate; HDR = high-dose-rate; BT = brachytherapy; NR = not reported.

Table 6 – Results of HDR brachytherapy boost series.

Institution	Patient no.	RT scheme (fraction no. × dose [Gy])	Median FUP (years)	5-Year LR %	Annual LR %	Exc./good cosmesis %
Barcelona[16]	294	8–11 × 2–2.5	5.8	9 (9-year)	1.00	96
University Wien[17]	274	1 × 7–12	8.7	3.9 (10-year)	0.39	38
Brno[18]	215	1 × 8–12	5.8	1.5	0.30	73
Linz[19]	212	1 × 10	5.2	4.6	0.92	78
Saarbrücken[20]	202	1 × 12–15	>3	6.4[a]	NA	85
TMH, Mumbai[21]	153	1 × 10	3	8	1.60	83
Valencia[23]	125	3 × 4.4	7	4.2	0.84	77
Paris[24]	108	2 × 5	3.75	5.1	1.02	63
University Rostock[25]	75	1 × 8–12	7.8	5.9 (10-year)	0.59	NR
Virgina C. University[27]	18	6 × 2.5	4.2	0	0	67
Present study	100	3 × 4–4.75; 1 × 8–10.35	7.8	7.0 (8-year)	0.88	56
All patients	1776		3–8.7	0–9	0–1.60	38–96

RT = radiotherapy; FUP = follow-up period; LR = local recurrence; TMH = Tata Memorial Hospital; NA = not applicable; NR = not reported.
[a] Crude rate.

6. Conclusions

Fractionated HDR BT boost using multi-catheter implants provides excellent long-term local tumour control with acceptable cosmetic outcome and low rate of grade 3 late radiation side effects. Our results confirm that high-dose HDR BT boost can mask classical risk factors for LR (with the exception of positive margins).

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